Remarks/Arguments

Claim 37 is canceled without prejudice. Claim 32 is amended. New claims 69-71 are added. Support for the amendment to claim 32 can be found, e.g., at page 3, lines 7-10 and page 16, lines 14-17 of the specification. Support for new claims 69-71 can be found, e.g., at page 3, lines 3-5 of the specification. No new matter is introduced.

Claims 32, 34-36, 38, 40-45, 55, 58-61, and 63-71 are pending in the application. Reexamination and reconsideration of the application, as amended, are respectfully requested.

Election/Restriction

Claim 37, directed to a non-elected species, is canceled without prejudice. Applicants understand that, once generic claim 32 is allowed, claim 37, dependent from claim 32, will be eligible for rejoinder under 37 C.F.R. § 1.141. Applicants respectfully request that claim 37 be examined once generic claim 32 is allowed.

Claim Rejections – 35 U.S.C. § 102

Claims 32, 34-35, 41-43, 55, 58-59, and 64-66 stand rejected as being anticipated by Alexeev et al. (Nature Biotech, 2000, 18:43-47; "Alexeev").

Applicants respectfully disagree with the Examiner. However, for the sole purpose of moving this application forward, claim 32 is amended to (1) clarify that the mRNA component in the mRNA-cDNA hybrid duplex is in the sense orientation and the cDNA component is in the anti-sense orientation, and (2) limit the length of the mRNA-cDNA hybrid duplex to more than 500 base pairs.

As mentioned in Applicants' Amendment dated March 27, 2006, Alexeev discloses a chimeric oligonucleotide that contains both ribonucleotides and

deoxyribonucleotides. The RNA components of this molecule, i.e., aauccaaacu and uuuccgcagu, are in the anti-sense orientation (Tyr-A in Figure 1). Further, the length of the RNA-DNA hybrid duplexes in this molecule is much less than 500 base pairs. Therefore, Alexeev cannot anticipate claim 32 because it fails to teach every limitation of claim 32.

New claim 69 requires that (1) the mRNA component in the mRNA-cDNA hybrid duplex is in the sense orientation and the cDNA component is in the anti-sense orientation, and (2) the mRNA is a full-length mRNA transcript of the targeted gene. As discussed above, the RNA components of the chimeric oligonucleotide in Alexeev are in the anti-sense orientation. Also, as shown by Figure 1 in Alexeev, the RNA components of the chimeric oligonucleotide are not full-length mRNAs. Therefore, Alexeev cannot anticipate claim 69 because it fails to teach every limitation of claim 69.

By the same token, claims 34-35, 41-43, 55, 58-59, and 64-66, dependent directly or indirectly from claim 32, are not anticipated by Alexeev, either. Likewise, new claims 70-71, dependent from claim 69, are not anticipated by Alexeev. Applicants respectfully request that the rejection be withdrawn.

Claim Rejections – 35 U.S.C. § 103(a)

Claims 32, 34-38, 40-45, 55, 58-61, and 63-68 stand rejected as being unpatentable over Alexeev in view of Fire et al. (U.S. Patent No. 6,506,559; "Fire") and Bennett et al. (U.S. Patent No. 6,066,500; "Bennett"). Applicants respectfully disagree with the Examiner.

As mentioned in Applicants' Amendment dated March 27, 2006, Fire discloses double-stranded RNA (dsRNA) for inhibiting expression of a target gene in a cell. There is no suggestion whatsoever in either Alexeev or Fire that the dsRNA taught by Fire should be replaced with the chimeric oligonucleotide taught by

Alexeev, let alone that the RNA components in Alexeev's chimeric oligonucleotide should be changed to the sense orientation and should have more than 500 bases or be a full-length mRNA transcript of the targeted gene.

The Examiner stated in the Office Action dated December 27, 2005:

> "One of ordinary skill in the art would have been motivated to substitute in the RNA-DNA hybrid of Alexeev et al. into the method of Fire, because the teachings of both authors are similar and overlap substantially in that both use double stranded nucleic acids to turn off unwanted gene expression and encourage the expression of the desired sequence. Furthermore, one of ordinary skill would have been motivated to substitute the RNA-DNA hybrid of Alexeev et al. in for the RNA-RNA hybrid of Fire et al. because the RNA-DNA hybrid of Alexeev et al. is more resistant to endogenous nuclease degradation, due to the presence of the DNA strand to said degradation."

Applicants respectfully disagree. Although RNA-DNA hybrid and RNA-RNA hybrid are both double-stranded nucleic acids, they inhibit the expression of a target gene through different mechanisms. More specifically, dsRNA-induced gene silencing as described in Fire requires formation of small double-stranded interfering RNAs (siRNA) for triggering mRNA degradation via a cellular mechanism, namely post-transcriptional gene silencing (PTGS) or RNA interference (RNAi), whereas gene silencing induced by a hybrid of an anti-sense RNA and a sense DNA as described in Alexeev does not generate siRNA in the process. Unlike the dsRNA, the hybrid of an anti-sense RNA and a sense DNA can directly interact with genomic DNA to modify the genomic DNA by cellular DNA repairing systems. As such, one of ordinary skill would not have been motivated to substitute Alexeev's chimeric oligonucleotide for Fire's dsRNA.

Further, it is a discovery of the present invention that a hybrid of a sense mRNA and an anti-sense cDNA can be used for gene silencing. This is achieved through yet another distinct mechanism. The hybrid of a sense mRNA and an anti-sense cDNA serves as a template for RNA polymerases type 2 to generate small

single-stranded RNA (microRNA) to interfere with the activation of gene transcription. Without the teaching of the present invention, one of ordinary skill in the art would not have been motivated to substitute Alexeev's chimeric oligonucleotide for Fire's dsRNA and, in the mean time, change the RNA components in Alexeev's chimeric oligonucleotide from the anti-sense orientation to the sense orientation. Also, without the teaching of the present invention, one of ordinary skill in the art would not have had a reasonable expectation of success for gene silencing by a hybrid of a sense mRNA and an anti-sense cDNA in view of Alexeev and Fire.

In addition, Fire recognizes that dsRNA has the advantage of stability (column 5, lines 15-19). Thus, one of ordinary skill would not have been motivated to substitute Alexeev's chimeric oligonucleotide for Fire's dsRNA for the stability purpose. Even if one of ordinary skill would have been motivated to do so, the RNA components of the RNA-DNA hybrid would have remained in the anti-sense orientation, since Fire does not teach otherwise.

Also as mentioned in Applicants' Amendment dated March 27, 2006, Bennett discloses anti-sense compounds, particularly oligonucleotides, which are targeted to a nucleic acid encoding β-catenin, and which modulate the expression of β-catenin. As such, Bennett cannot cure the defect of Alexeev and Fire, and was not relied upon by the Examiner for such. Instead, the Examiner cited Bennett merely for teaching pathogenic, viral, or oncogenic targets (the Office Action dated December 27, 2005).

Moreover, as mentioned in Applicants' Amendment dated March 27, 2006, a hybrid of a sense RNA and an anti-sense DNA has advantages over a hybrid of an anti-sense RNA and a sense DNA, a dsRNA, and an anti-sense oligonucleotide unexpected by Alexeev, Fire, and Bennett. Without such knowledge, one skilled in

the art would not have been motivated to combine Alexeev, Fire, and Bennett to come up with the present invention.

In light of the foregoing, Applicants respectfully submit that Alexeev, Fire, and Bennett, alone or in combination, cannot render claim 32 or 69 obvious, because the cited references fail to teach or suggest the mRNA-cDNA hybrid duplex of the present invention, its unexpected advantages, or a reasonable expectation of success for the claimed method.

By the same token, claims 34-38, 40-45, 55, 58-61, and 63-68, dependent directly or indirectly from claim 32, are also patentable over Alexeev, Fire, and Bennett. Likewise, new claims 70-71, dependent from claim 69, are non-obvious over the cited art. Withdrawal of the rejection is thus respectfully requested.

CONCLUSION

Applicants believe that the foregoing amendment complies with the requirements of form and thus should be admitted under 37 C.F.R. § 1.116(b). Alternatively, where the amendment is deemed to touch the merits, admission is requested under 37 C.F.R. § 1.116(c). Lastly, admission is requested under 37 C.F.R. § 1.116(b) as presenting rejected claims in better form for consideration on appeal.

In view of the foregoing, it is respectfully submitted that the application is in condition for allowance. Reexamination and reconsideration of the application, as amended, are requested.

If for any reason the Examiner finds the application other than in condition for allowance, the Examiner is requested to call the undersigned attorney at the Los Angeles, California telephone number (213) 337-6700 to discuss the steps necessary for placing the application in condition for allowance.

If there are any fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-1314.

Respectfully submitted,
HOGAN & HARTSON L.L.P.

Date: September 12, 2006

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